Restor Neurol Neurosci. 1998;13(1,2):3-10.

Glutamate Antagonists in Therapy of Stroke.

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It is well established that excitotoxicity is a key mechanism of tissue destruction in focal cerebral ischemia (stroke). Very soon after onset of a critical perfusion deficit energy failure leads to neuronal depolarization and release of excitatory aminoacids, most notably glutamate. At the same time, energy dependent reuptake of excitatory amino acids is impede. Overstimulation of glutamate receptors (NMDA, AMPA/kainate, metabotropic) induces dramatically increased intracellular Ca2+ concentrations, release of K+ into the extracellular space, and cell swelling due to the passive movement of water with Na+ influx. The massively increased intracellular second messenger Ca2+ triggers numerous deleterious processes, including free radial formation and membrane degradation, mitochondrial dysfunction, inflammation, DNA-damage and apoptosis. A plethora of experimental studies have convincingly demonstrated the relevance of excitotoxicity in focal cerebral ischemia, and pointed to very effective experimental treatment strategies, many of which involve the blockade of glutamate receptors. Unfortunately, large clinical studies were so far unable to replicate the animal data in human stroke patients. This article, by reviewing excitotoxic damage of focal cerebral ischemia in the context of a complex pathophysiological cascade, aims at explaining this failure and stimulating further efforts in drug design and clinical evaluation to establish the first neuroprotective therapy of human stroke.

PMID: 12671283 [PubMed - as supplied by publisher]